Design & Classification of Trials

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Written Protocol Specifies Design

Clinical hypothesis:	**Patient selection**
	Intervention and Control
	Outcome/Endpoint (Timeframe)
Statistical issues:	**Design**
	Masking
	Randomization
	Sample size
	Interim monitoring
	Analysis strategy
Procedural:	**Data Collection/Forms**
	Data Management
	Quality Control
	Organization and Administration

Design & Classification of Trials

- No perfect design
- No design fits all needs and circumstances
- First select research objective, then choose design

Parallel Design

Group I on Treatment A

Group II on Treatment B

Group III on Treatment C

Parallel Design

- Disadvantages
  - Inefficiency in:
    - Size
    - Time
    - Cost
    - Number of Questions
- Advantages
  - Simple
  - Few Assumptions
  - Valid Comparisons
  - Can be used in all situations

Positive Control

Group I on Standard TX

Group II on New TX

Positive Control

- **Advantages**
  - Assess whether new treatment as good as or better than standard
  - Avoid Placebo/ethical issue
- **Disadvantages**
  - Power issue
  - Possible lack of benefit of standard treatment

Crossover Design

Group I on TX A, Then TX B

Group II on TX B, Then TX A

Crossover Design

- **Advantages**
  - Sample size:
  - Use same subject twice - reduce variability
  - Appealing to use a patient as his/her own control
  - Good for eyes, dermatology
- **Disadvantages**
  - Assumption of no carryover effect (Particularly tricky/behavorial intervention)
  - Stability of disease process
  - Limits response variable

Can't use "Cure" or Clinical Event

Factorial Design

	Treatment A	Control
Treatment B	a	b
Control	c	d

Treatment A & B
Treatment A only
Treatment B only
Neither

Factorial Design

- **Advantages**
  - Answer two (or more) questions at the same time
  - Get information on interaction
  - Get information whether two treatments are better than one
- **Disadvantages**
  - Generally low power to detect interaction
  - Between cell comparisons have fewer numbers
  - Complexity
  - Impact on recruitment
  - Impact on compliance
  - Can you change 2 behaviors simultaneously?
- **Nevertheless, this is an underused design!**

Physician Health Study (PHS)

- Factorial trial: Aspirin for heart disease and Betacarotene for cancer incidence (except non-melanoma skin cancer)
- 22,000 U.S. physicians
- Average of 12 years of follow-up
- Aspirin efficacious for cardiovascular endpoint - stopped early

Physician's Health Study (PHS)

	Beta Carotene	Placebo	RR	CI
N	11,036	11,035		
Malignant Neoplasm	1,273	1,293	.98	(.91, 1.06)
Cancer Deaths	386	380	1.02	(.89, 1.18)

Group Allocation Designs

- Treatment is applied to entire community instead of individual patient.
- Assign at random hospitals, clinics, factories, cities, or classrooms.
- Examples:

  public access defibrillators
  media comparisons to get people to act quickly if experience heart attack symptoms
  community smoking cessation, weight control, exercise.

Group Allocation Designs

- **Advantages**
  - Avoid contamination
  - Allow use of mass interventions
- **Disadvantages**
  - Effective sample size less than number of individuals
  - Statistically outcomes from two people from a community are correlated (intra class correlation)
  - Likely to result in very large number of individuals
- **Different statistical analyses methods required**

Explanatory versus Management (Efficacy vs. Effectiveness)

Can drug A reduce tumor size?

Does prescribing drug A to patients with tumors do more good than harm?

Efficacy versus Effectiveness

- Efficacy clinical trials show that a treatment can work
- Evidence suggests that interventions are often less effective in clinical settings than in the laboratory (Weisz et al, 1992)
- Effectiveness trials evaluate treatments in the settings where they will be applied.

NHLBI, NCI Research Phases

- hypothesis generation (phase I)
- method development (phase II)
- controlled intervention trials (phase III)
- studies in defined populations (phase IV)
- demonstration research (phase V)

Drug Trials

Phase I	Healthy Volunteers
Phase II	Safety & Efficacy
*Phase III	Comparative
Phase IV	Post-Market Surveillance

Mega Trials = Large Simple Trials

- **Advantages**
  - Quick answers
  - Important public health issues
  - Entire community involvement
  - Moderate effects
- **Disadvantages**
  - "Hard" endpoints only
  - Few secondary questions
  - No quality control
  - Only common diseases

Masking (blinding)

Single

Double

- Not possible w/behavior trials
- Masked evaluation key to minimize bias
- Deception not ethical